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10/562,807	07/06/2006	David Paul Humphreys	07-1047-WO-US	6569

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EXAMINER
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BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
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1643

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/562,807	<b>Applicant(s)</b> HUMPHREYS ET AL.	
	<b>Examiner</b> DAVID J. BLANCHARD	<b>Art Unit</b> 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 15 October 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-26, 29 and 30 is/are pending in the application.
- 4a) Of the above claim(s) 19-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-18 and 29-30 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>10/15/09</u> . | 6) <input type="checkbox"/> Other: _____  |

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### **DETAILED ACTION**

1. Claims 27-28 have been cancelled.
2. Claims 19-26 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.
3. Claims 1-18 and 29-30 are under consideration.

### ***Objections/Rejections Withdrawn***

4. The objection to the disclosure as not containing a paper copy of the sequence listing is withdrawn in view of applicants' submission of the paper copy of the sequence listing and the statements that the paper copy and the computer readable form are the same and introduce no new matter.

### ***Rejections Maintained***

#### ***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The rejection of claims 1-7, 10-18 and 29-30 under 35 U.S.C. 103(a) as being unpatentable over Chapman et al (Nature Biotechnology, 17:780-783, 1999, IDS reference 4 filed 10/10/06) in view of Humphreys et al (Journal of Immunological Methods, 209:193-202, 1997, IDS reference 11 filed 10/10/06) is maintained.

Chapman et al teach that the random attachment of PEG to Fab' fragments results in conjugate heterogeneity and reduced antigen binding, however, Chapman et al teach that site-specific attachment of PEG molecules (e.g., PEG-maleimide of 5 kDa, 25 kDa and 40 kDa) to Fab' fragments at one or two engineered hinge cysteine residues retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of one or two defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up and should allow for rapid and economic production of therapeutic antibodies for chronic disease therapy (see entire document, particularly abstract, and pp. 780-781). Chapman et al do not specifically teach wherein the interchain cysteines of the CH1 (residue 233) and CL (residue 214) of the Fab' fragments are mutated to serines or wherein the modified hinge region comprises SEQ ID NO:1, SEQ ID NO:2, or comprises SEQ ID NO:3 or SEQ ID NO:4. These deficiencies are made up for in the teachings of Humphreys et al.

Humphreys et al teach the production of Fab' fragments comprising the hinge sequences of SEQ ID Nos:1, 2 or 3 wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds between hinge regions and other cysteines and removal of the inter CL-CH1 disulfide bond from the Fab' accelerated and simplified the

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construction of the Fab' fragments and did not affect Fab' stability (see entire document, particularly pp. 194-195, 201 and Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an antibody fragment comprising a Fab' fragment in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the antibody fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID Nos:1, 2 or 3) for PEGylation as well as pharmaceutical compositions comprising said antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer for chronic disease therapy.

One of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have produced an antibody fragment comprising a Fab' fragment in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the antibody fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID Nos:1, 2 or 3) for PEGylation as well as pharmaceutical compositions comprising said antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer for chronic disease therapy in view of Chapman et al and Humphreys et al because Chapman et al teach that the random attachment of PEG to Fab' fragments results in conjugate heterogeneity and reduced antigen binding, however, the site-specific attachment of PEG molecules (e.g., PEG-maleimide of 5 kDa, 25 kDa and 40 kDa) to Fab' fragments at one or two engineered hinge cysteine residues retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of one or two defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up and should allow for rapid and economic production of therapeutic antibodies for chronic disease therapy and Humphreys et al teach the production of Fab' fragments comprising the hinge sequence of SEQ ID Nos:1, 2 or 3 wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds between the hinge regions and other cysteines and removal of the inter CL-CH1 disulfide bond from the Fab' accelerated and simplified the construction of the Fab' fragments and did not affect Fab' stability. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce site-specific PEGylated

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Fab' fragments wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds, to simplify and accelerate the construction of the Fab' fragments using the hinge peptides of Humphreys (e.g., identical to SEQ ID Nos:1, 2 or 3) for PEG attachment since site-specific attachment of PEG molecules at one or two hinge cysteine(s) retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of one or two defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up, allowing for rapid and economic production of therapeutic antibodies for chronic disease, thereby overcoming conjugate heterogeneity and reduced antigen binding associated with random attachment of PEG to Fab' fragments according to Chapman et al. Thus, there would be several advantages to producing antibody fragments comprising a Fab' fragment lacking the interchain CL-CH1 cysteines and modified by site-specific attachment of at least one PEG molecule at the cysteine residue(s) within the hinge peptide of SEQ ID NO:1, 2 or 3. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Chapman et al provides evidence that site-specific attachment of PEG molecules to hinge cysteines of Fab' fragments does not reduce antigen binding and removal of the inter CL-CH1 disulfide bond accelerated and simplified the construction of the Fab' fragments and did not affect Fab' stability. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced an antibody fragment comprising a Fab' fragment in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the antibody fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID Nos:1, 2 or 3) for PEGylation as well as pharmaceutical compositions comprising said antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer for chronic disease therapy in view of Chapman et al and Humphreys et al.

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Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

### ***Response to Arguments***

The response filed 10/15/2009 states that Chapman et al teach an intact covalent bond between the light and heavy chains, thus teaching away from the presently claimed invention. Applicant states that Humphreys is directed towards the production of dimeric Fab' and examines the effects of various parameters, including hinge size and isotype, presence of interchain disulfide bond, Fab' expression levels, tail piece sequences and growth conditions. Humphrey's teaches away from modification of the hinge region. Applicant submits that the instant rejection is based on impermissible hindsight. Applicant argues that the goals of Chapman and Humphreys are different and there is no reason why one skilled in the art interested in producing PEGylated antibody fragments would have turned to the disclosure of Humphrey's et al.

Applicants' arguments have been fully considered but are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants' argument that the teachings of Chapman et al and Humphreys et al are not combinable since Chapman et al do not teach any modification to either the light chain or the heavy chain of the Fab' fragment and since Humphreys doesn't teach modification of Fab' fragments having an effector molecule (e.g., PEG) errors in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way that deny factfinders recourse to common sense. KSR, 550 U.S. at \_\_\_, 82 USPQ2d at 1391. The "obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, or motivation, or by overemphasis on the importance of published articles and explicit content of issued patents." *Id.* at 1741. "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." KSR, 550 U.S. at \_\_\_, 82 USPQ2d at 1397. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences

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and creative steps that a person of ordinary skill in the art would employ.”Id. at \_\_\_, 82 USPQ2d at 1396. In the instant case, the teachings of Chapman et al indicate that the random attachment of PEG to Fab' fragments results in conjugate heterogeneity and reduced antigen binding, however, the site-specific attachment of PEG molecules (e.g., PEG-maleimide of 5 kDa, 25 kDa and 40 kDa) to Fab' fragments at one or two engineered hinge cysteine residues retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of one or two defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up and should allow for rapid and economic production of therapeutic antibodies for chronic disease therapy. While Chapman et al does not teach mutation of the interchain cysteines of the CH1 and CL or the modified hinge sequences, however, Humphreys et al teach the production of Fab' fragments comprising the hinge sequence of SEQ ID Nos:1, 2 or 3 wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds between the hinge regions and other cysteines and removal of the inter CL-CH1 disulfide bond from the Fab' accelerated and simplified the construction of the Fab' fragments and did not affect Fab' stability. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce site-specific PEGylated Fab' fragments wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds, to simplify and accelerate the construction of the Fab' fragments using the hinge peptides of Humphreys (e.g., identical to SEQ ID Nos:1, 2 or 3) for PEG attachment since site-specific attachment of PEG molecules at one or two hinge cysteine(s) retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of one or two defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up, allowing for rapid and economic production of therapeutic antibodies for chronic disease, thereby overcoming conjugate heterogeneity and reduced antigen binding associated with random attachment of PEG to Fab' fragments according to Chapman et al. Thus, there would be several advantages to producing antibody fragments comprising a Fab' fragment lacking the interchain CL-CH1 cysteines and modified by site-specific attachment of at least one PEG molecule at the cysteine residue(s) within the hinge peptide of SEQ ID NO:1, 2 or 3. The fact that Humphreys was concerned with

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a different problem or goal does not obviate a finding of obviousness because Humphreys et al clearly teach the advantages of Fab' fragment lacking the interchain CL-CH1 cysteines, e.g., removal of the interchain CL-CH1 cysteines minimizes incorrect interchain disulfide bonds between the hinge regions and other cysteines and accelerates and simplifies the construction of the Fab' fragments and did not affect Fab' stability. Furthermore, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

7. The rejection of claims 1 and 8-9 under 35 U.S.C. 103(a) as being unpatentable over Singh et al (Analytical Biochemistry, 304(2):147-156, May 15, 2002, cited on PTO-892 mailed 3/5/08) in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 42 filed 10/10/06) and Humphreys et al (Journal of Immunological Methods, 209:193-202, 1997, IDS reference 11 filed 10/10/06) is maintained.

Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and selenol-catalyzed reduction of disulfide bonds in Fab fragments has previously been reported (see entire document, particularly abstract, pp, 148, 154-155 and Fig. 1). Singh et al do not specifically teach an antibody comprising a Fab' fragment comprising a hinge region containing one or two cysteines and wherein the Fab' fragment has been modified by attachment of at least one PEG or PEG

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derivative wherein both the interchain cysteine of CL and the interchain cysteine of CH1 have been replaced with another amino acid such that the heavy chain in the fragment is not covalently bonded to the light chain. These deficiencies are made for in the teachings of Hesi et al and Humphreys.

Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> (e.g., antibody fragment comprising Fab') fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules, and wherein the disulfide bridge linking the heavy and light chains is avoided by substituting the cysteine residue of the heavy or light chain with serine and the PEG molecules are attached via a cysteine residue or residues engineered into a selected site or selected sites in the antibody fragment as well as pharmaceutical compositions comprising the anti-IL-8 antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer (see entire document, particularly pp. 20, lines 29-37, pp. 21-27, 37-38, 42, 98-102 and 104-105).

Humphreys et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> fragments in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID No:1, 2 or 3) as well as a cysteine residue or residues engineered into a selected site or sites in the antibody fragment (i.e., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides as taught by Singh et al for therapeutic benefit of inflammatory disorders.

One of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> fragments in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID No:1, 2 or 3) as well as a cysteine residue or residues engineered into a selected site or sites in the antibody fragment (i.e., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides for therapeutic benefit of inflammatory disorders in view of

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Singh et al and Hesi et al and Humphreys et al because Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> (e.g., antibody fragment comprising Fab') fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules, and wherein the disulfide bridge linking the heavy and light chains is avoided by substituting the cysteine residue of the heavy or light chain with serine and the PEG molecules are attached via a cysteine residue or residues engineered into a selected site or selected sites in the antibody fragment and Humphreys et al teach the production of Fab' fragments comprising the hinge sequences of SEQ ID Nos:1, 2 or 3 wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds between hinge regions and other cysteines and removal of the inter CL-CH1 disulfide bond from the Fab' accelerated and simplified the construction of the Fab' fragments and did not affect Fab' stability. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> fragments lacking the CL-CH1 interchain disulfide and comprising a hinge peptide containing one or two cysteines (e.g., SEQ ID No:1, 2 or 3) as well as cysteine residues engineered into selected sites in the antibody fragment (e.g., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides as taught by Singh et al since selenol-catalyzed reduction of interchain disulfides provides a rapid method in which the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and the method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1,

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5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Singh et al provides evidence that reduction of interchain disulfide bonds of an antibody does not result in a significant decrease in affinity or stability and selenol-catalyzed reduction of disulfide bonds in Fab fragments has been performed previously (Singh et al, pg. 148 1<sup>st</sup> col.). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> fragments in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID No:1, 2 or 3) as well as a cysteine residue or residues engineered into a selected site or sites in the antibody fragment (i.e., in both the heavy and light chain constant regions) for PEGylation according to the selenol-catalyzed reduction of disulfides for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

### ***Response to Arguments***

The response filed 10/15/09 reiterates that at the time of the priority of the present application, one skilled in the art would not have attempted to attached PEG (or a derivative) to the interchain cysteines of a Fab' fragment because of the risk that the PEG would create a destabilizing effect on the fragment that would force the heavy and light chains apart. Applicant argues that the labels of Singh are very different from the presently recited effector molecules (PEG). One skilled in the art could not predictably extrapolate the teachings of Singh using small molecules with whole antibodies to the use of large effector molecules with Fab' antibody fragments. Applicants' arguments have been fully considered but are not found persuasive. Again, Applicants' arguments questioning the operability of the prior art, i.e., that PEGylation of the interchain cysteines would destabilize the antibody fragment and force the heavy and light chains apart, and one of ordinary skill in the art could not predictably rely on the teachings of Singh, applicant is reminded that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of

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attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). See MPEP 716.01(c).

Applicant also argues that Singh et al only describes the attachment of small molecules such as biotin to *a whole antibody*, not larger molecules such as PEG and Hesi teaches fragments in which one of the interchain cysteines has been substituted with serine, and no more than one polymer is attached to the fragment, the attachment being at the remaining interchain cysteine. Hesi et al does not suggest that both the heavy and light interchain cysteines are to be replaced with another amino acid, nor does Hesi suggest any reason for doing so. As discussed above, applicant states that Humphreys is concerned with the production of dimeric F(ab')<sub>2</sub> fragments containing a specific hinge sequence having four cysteines and wherein *both* interchain cysteines have been replaced with serines and Humphreys makes no mention of fragments in which both the interchain cysteines were retained and have effector molecules attached and thus, combining Singh, Hesi and Humphreys would not result in the claimed structure. Applicant also states that Humphreys et al is specifically directed to using Fab' fragments to make F(ab')<sub>2</sub> fragments, which are excluded from the scope of the present claims. Applicants' arguments have been fully considered but are not found persuasive. In response to applicants' statement that the instant claims exclude F(ab')<sub>2</sub> fragments, applicant is reminded that the transitional term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, MEP 2111.03. Thus, the recitation "An antibody fragment comprising a Fab' fragment..." (claim 1) is inclusive to the F(ab')<sub>2</sub> fragments of Humphreys et al, since a F(ab')<sub>2</sub> can be split into two Fab' fragments by mild reduction and therefore, a F(ab')<sub>2</sub> is merely one interpretation of "An antibody fragment comprising a Fab' fragment...". In response to applicant's arguments against

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the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, in response to applicants' arguments that Singh et al is directed to total PEGylation of whole antibody molecules whereas Hesi is directed towards selective PEGylation and the attachment of one polymer wherein attachment is at the interchain cysteine that is not substituted and that Humphreys is directed to making F(ab')<sub>2</sub> fragments and teaches nothing about effector molecules, applicant is reminded that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). See also *In re Sneed*, 710 F.2d 1544, 1550, 218 USPQ 385, 389 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review."); and *In re Nievelt*, 482 F.2d 965, 179 USPQ 224, 226 (CCPA 1973) ("Combining the teachings of references does not involve an ability to combine their specific structures."). The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 USPQ 545 (CCPA 1969). In this case, while Hesi et al does teach certain embodiments wherein the fragment is a F(ab')<sub>2</sub> comprising two polymer molecules attached and Fab, Fab', or Fab'-SH wherein only one polymer molecule is attached, Hesi et al also teach additional embodiments wherein the fragment is a Fab, Fab' or Fab'-SH wherein the conjugate contains no more than about 10 polymer molecules, or no more than 5 polymer molecules, or no more than about 4 polymer molecules, or no more than about 3 polymer molecules, or no more than about 2 polymer molecules, or no more than about 1 polymer molecule (e.g., see at least pg. 23, line 15-pg. 24, line 23, pp. 28-30, pg. 30, lines 30-36). Thus, the teachings of Hesi et al are clearly not limited to the attachment of one polymer wherein attachment is at the interchain cysteine that is not substituted as suggested by applicant.

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It is reiterated that Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules (, i.e., the antibody is attached to 10 or fewer PEG molecules, attached to about 5 or fewer PEG molecules, attached to about 4 or fewer PEG molecules, attached to about 3 or fewer PEG molecules (e.g., pp. 28-29)) via a cysteine residue or residues engineered into the hinge region wherein each PEG molecule may be 20,000 Da or 30,000 Da and Humphreys teach Fab' hinge region peptides (i.e., SEQ ID Nos:1-3) that efficiently generates dimer (e.g., di-Fab), and the modified hinge peptides can be reduced to expose reactive thiols to which one, two, three or more effector molecules, including PEG may be attached. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> fragments comprising the cysteine containing hinge peptides of SEQ ID Nos:1-3 as taught by Humphreys and reduced using the selenol-catalyzed reduction of interchain disulfides to expose reactive thiols to which PEG molecules are attached since selenol-catalyzed reduction of interchain disulfides provides a rapid method in which the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and the method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Applicants' remarks regarding Chapman et al are acknowledged (*it is noted that Chapman is not relied upon in the instant rejection*), however, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Singh et al provides evidence

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that reduction of interchain disulfide bonds of an antibody by selenol-catalyzed reduction provides more predictable homologous incorporation of labeled groups, is not inhibited by the presence of amines in solution and does not result in a significant decrease in affinity or stability, and selenol-catalyzed reduction of disulfide bonds in Fab fragments has been performed previously (Singh et al, pg. 148 1<sup>st</sup> col.). Applicant is reminded that obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')<sub>2</sub> fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

### ***Double Patenting***

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. The rejection of claims 1-7, 10-11, 13, 15-18 and 29-30 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of Chapman et al (Nature Biotechnology, 17:780-783, 1999, IDS reference 4 filed 10/10/06) and Humphreys et al (Journal of Immunological Methods, 209:193-202, 1997, IDS reference 11 filed 10/10/06) is maintained.

Claims 7 and 10 of U.S. Patent No. 6,642,356 B1 are drawn to a Fab or Fab' fragment comprising one polypeptide chain that comprises the amino acid sequence of SEQ ID NO:1 (e.g., TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the Fab or Fab' fragment has one or more effector or reporter molecules attached to it. Claims 7 and 10 of U.S. Patent No. 6,642,356 B1 do not specifically teach wherein the interchain cysteines of the CH1 and CL are substituted with serine and wherein the effector molecule is PEG, or pharmaceutical compositions comprising the Fab or Fab' fragment and a pharmaceutically acceptable carrier or excipient. These deficiencies are made up for in the teachings of Chapman et al and Humphreys et al.

Chapman et al have been described supra.

Humphreys have been described supra.

The claims in the instant application are obvious variants of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a Fab or Fab' fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the CH1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for chronic disease therapy.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a Fab or Fab' fragment

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comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the C<sub>H</sub>1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for chronic disease therapy in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Chapman et al and Humphreys et al because Chapman et al teach that the random attachment of PEG to Fab' fragments results in conjugate heterogeneity and reduced antigen binding, however, site-specific attachment of PEG molecules (e.g., PEG-maleimide of 5 kDa, 25 kDa and 40 kDa) to Fab' fragments at engineered hinge cysteine residues retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up and should allow for rapid and economic production of therapeutic antibodies for chronic disease therapy according to Chapman et al and Humphreys et al teach the production of Fab' fragments wherein the interchain CL-CH1 cysteines are mutated to serines to minimize incorrect interchain disulfide bonds between hinge regions and other cysteines and removal of the inter CL-CH1 disulfide bond from the Fab' accelerated and simplified the construction of the Fab' fragments and did not affect Fab' stability. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce a Fab or Fab' fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the C<sub>H</sub>1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for immunotherapy since site-specific attachment of PEG molecules at hinge cysteines retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up, allowing for rapid and economic production of therapeutic antibodies for chronic disease, thereby overcoming conjugate heterogeneity and reduced antigen binding associated with random attachment of PEG to Fab' fragments according to Chapman et al. Thus, it would have been

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*prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a Fab or Fab' fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the C<sub>H</sub>1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for chronic disease therapy in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Chapman et al and Humphreys et al.

Claims 1-7, 10-11, 13, 15-18 and 29-30 are directed to an invention not patentably distinct from claims 7 and 10 of commonly assigned U.S. Patent No. 6,642,356 B1. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,642,356 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

### ***Response to Arguments***

The response filed 10/15/2009 states that the amino acid sequence in the claims of the '356 patent are not the same as the amino acid sequences of the present application. This has been fully considered but is not found persuasive. The rejected claims do not recite or require

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any particular sequence and do not exclude the sequence of the '356 patent. Thus, the sequence of the '356 patent claims reads upon the broader scope of the instant claims.

Applicant argues that whether or not it would have been obvious to produce a Fab' fragment with SEQ ID NO:1 of the '356 patent is irrelevant to the question of whether the presently claimed invention is obvious and the present claims encompass embodiments wherein there are free cysteine thiols that are not attached to PEG molecules. The present invention is based on applicants' surprising discovery that a Fab' fragment could be produced having affinity for antigen comparable to wild type antibody, yet have no disulfide bridge between the heavy and light chains. There is no motivation to look to the teachings of Chapman et al and Humphreys et al because nothing in any of these references suggests that it would be desirable to have a Fab' fragment with no interchain bonds between the heavy and light chains. Applicants' arguments have been fully considered but are not found persuasive. The appropriate question at issue is whether or not it would have been obvious to modify the Fab or Fab' fragments of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 to substitute the interchain cysteines of the C<sub>H</sub>1 and CL with serines and attach PEG molecules to the free cysteine thiols of SEQ ID NO:1. In the instant case, the ordinary skilled artisan would have been motivated to modify the Fab or Fab' fragments of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 since site-specific attachment of PEG molecules (e.g., PEG-maleimide of 5 kDa, 25 kDa and 40 kDa) to Fab' fragments at engineered hinge cysteine residues retain full antigen-binding activity, have increased *in vivo* half-lives, improved pharmacokinetic profiles over whole IgG and the use of defined PEG attachment sites facilitates the production of well-defined conjugates that are identical from batch to batch and simple to scale up and should allow for rapid and economic production of therapeutic antibodies for chronic disease therapy and mutating the interchain CL-CH1 cysteines to serines minimizes incorrect interchain disulfide bonds between hinge regions and other cysteines and removal of the inter CL-CH1 disulfide bond from the Fab' accelerates and simplifies the construction of the Fab' fragments and did not affect Fab' stability. Thus, one or ordinary skill in the art would have been motivated to modify the Fab or Fab' fragments of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of the benefits made explicit in the teachings of Chapman et al and Humphreys et al. Further, in view of the teachings of Humphreys et al that removal of the inter CL-CH1 disulfide bond from the Fab' accelerates and

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simplifies the construction of the Fab' fragments and did not affect Fab' stability and site-specific attachment of PEG molecules at hinge cysteines retain full antigen-binding activity, one of ordinary skill in the art would have expected comparable binding relative to the wild type fragment.

For these reasons and those already of record the rejection is maintained.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/

Primary Examiner, A.U. 1643